

REMARKS

In accordance with 37 C.F.R. §1.121, a marked up copy of the presently amended specification paragraphs and claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing. Support for the additions and deletions can be found throughout the originally filed specification. Support for the new claims can be found throughout the originally filed specification, including the originally filed claims specifically. Specifically, support for new claim 11 can be found, for example, on page 55, lines 12-15, of the specification.

Notice of Draftperson's Patent Drawing Review

The drawings filed with the subject application were objected to in the Notice of Draftperson's Patent Drawing Review attached to the Office Action mailed July 16, 2002. Corrected drawings are being filed herewith, which Applicants submit overcome this objection. Withdrawal of the objection is, thus, respectfully requested.

Objections to the Specification

The Patent Office asserted that the following terms should be spelled out in full at the first instance of use: GLP-1, RP-HPLC, IRMA, and AUC. Further, the Patent Office asserted that the phrase "glutamic side chain" should be changed to "the glutamic acid side chain."

In order to expedite prosecution, the requested spellings changes are being made. The full name associated with each of the indicated terms has now been inserted in the specification and "acid" was inserted in the indicated phrase. Although these abbreviations are well known to those

of skill in the art, they are inserted in the specification for the Examiner's convenience. These alterations do not relate to patentability and are not being made for any reason related to patentability.

The 35 U.S.C. §112, First Paragraph, Rejection

Claims 7 and 8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for using conjugated exendin peptides (*e.g.*, a modified exendin or exendin agonist linked to one or more polyethylene glycol polymers) for treating glucagonoma syndrome that is characterized by a necrolytic migratory erythematous rash. The Examiner references Bloom et al., Am. J. Med., 82(Supp 5B):25-36 (1987) in this regard. The Examiner confirms, however, that the specification is enabling for "conjugating PEG polymer to the claimed exendin peptides and use of the conjugated exendin peptides for suppressing glucagon secretion in human with type 2 diabetes and decreasing glucagon secretion during hyperglycemic clamps in a diabetes-related disorder in human. This rejection is respectfully traversed.

The Examiner refers to the specification as allegedly not providing a working example, a description regarding the therapeutic background of disorders or diseases including glucagonoma and glucagonoma-related necrolytic migratory erythema, or therapeutic doses and administering approaches applicable to the disorders or diseases, as further alleged bases in regard to this rejection. See page 4, second paragraph, of the July 16, 2002, Office Action. The Examiner also alleges there to be an "unpredictable number of the PEG-exendin conjugate variants" and "unpredictability of biological half-life of the conjugates when administered." Based on these allegations, the Examiner

asserts that "the amount and level of experimentation needed is undue." Applicants respectfully disagree for the following reasons.

1. Working Examples Are Provided

The Manual of Patent Examining Procedure (MPEP) properly reiterates the law that, "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic'." MPEP §2164.02. As long as the invention is disclosed in such a manner to allow one skilled in the art to practice the invention without undue experimentation, the enablement requirement is fulfilled. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Likewise, the Court of Appeals for the Federal Circuit has ruled that the existence of working examples is only one of several factors to be considered in assessing enablement of a claimed invention. *In re Wands*, 858 F.2d 731, 737, 740 (Fed. Cir. 1988).

Despite the fact that working examples are not required under the law, the present specification does provide working examples of the invention. As noted by the Patent Office, Examples 4 and 5 of the present application teach decreasing glucagon secretion during hyperglycemic clamp experiments, as well as reducing plasma glucose concentrations in type 2 diabetics (page 4, last paragraph, of the July 16, 2002, Office Action). Indeed, the Patent Office has itself noted that the specification "shows the peptide mediated decrease of plasma glucagon, and sets forth example[s] for [showing the] effect of the exendin peptide on glucagon secretion in people with type 2 diabetes" (Paragraph bridging pages 5-6 of the July 16, 2002, Office Action).

Further, Applicants teach that the invention in general “relates to methods for lowering glucagon levels and/or suppressing glucagon secretion in a subject . . . [and] to the treatment of hyperglucagonemia and conditions that benefit from administration of glucagonostatic agents, including but not limited to necrolytic migratory erythema.” *See, e.g.*, page 8, lines 20-25, of the specification. Given these teachings, there is no reason to doubt that one skilled in the art would be able to practice the full scope of the claimed invention. One skilled in the art would consider that methods for treating well known glucagonoma and glucagonoma-related necrolytic migratory erythema according to the present invention would also be successful as they are also taught to benefit from the administration of glucagonostatic agents. The Examiner has not offered any evidence to rebut Applicants’ teachings in this regard.

2. *The Specification Does Describe the Therapeutic Background of Glucagonoma and Glucagonoma-Related Necrolytic Migratory Erythema*

The Examiner asserts that the specification “is silent as to therapeutic background of the relation of suppression of plasma glucagon to glucagonoma or glucagonoma-related necrolytic migratory erythema.” According to the Examiner the skilled artisan therefore “cannot envision what is therapeutic relationship between glucagonoma or glucagonoma-related necrolytic migratory erythema and exendin biological activity” (see the paragraph bridging Pages 4 and 5 of the July 16, 2002, Office Action). The Examiner further alleges that the specification is silent as to “teachings and supports (including medical and therapeutically background) for the claimed disorders” (Page six, first paragraph, of the July 16, 2002, Office Action).

As noted by the Patent Office, the law which is applicable to the Examiner's assertions is as follows:

A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

MPEP §2164.01. In this regard, the Examiner's attention is drawn to page 7, last paragraph, of the specification, for example, which discusses glucagonoma, a condition which produces glucose intolerance and necrolytic migratory erythema, a scaly red rash, sometimes blistering and eventually crusting, localized to the face, abdomen, extremities and perineum. The condition, which was first described several decades ago and clearly within the general knowledge of those of ordinary skill in the art, is also described therein as responding to glucagonostatic agents, a class in which the compounds of claimed methods have been found to be included. The law does not require that Applicants teach any more than is in the specification in order to satisfy the requirements of 35 U.S.C. §112, first paragraph.

Glucagonoma and glucagonoma-related necrolytic migratory erythema, including conventional treatments therefor, are within the general knowledge of those of ordinary skill in the art. This general knowledge need not be narrated within the present specification in order to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Nevertheless, in the specification, Applicants note that these conditions are known to respond to glucagonostatic agents, a class in which the compounds of claimed methods have been found to be included based, for example, on their ability to suppress glucagon secretion. Thus, the therapeutic relationship between suppression

of plasma glucagon and glucagonoma or glucagonoma-related necrolytic migratory erythema is in fact described in the specification.

3. *The Specification Does Describe Therapeutic Doses and Means of Administration Applicable to Glucagonoma and Glucagonoma-Related Necrolytic Migratory Erythema*

Applicants again note the law that dictates that a patent specification need not include, and preferably excludes, what is well known to those within the art. *Buchner, Hybritech, Lindemann, supra*. In this regard, Applicants note that page 55, lines 24-29, of the specification teach: "As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition, the glucagon level or level of inhibition of glucagon suppression to be obtained, and other factors." Despite the fact that the law requires no more in this regard, page 56, first and second paragraphs, teach effective daily anti-glucagon doses of compounds used in the claimed methods. Applicants further note that the "exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual." Thus, the specification provides adequate guidance for practice of the present invention, which exact methods employed are determined by those skilled in the art, e.g., clinicians employing the methods during treatment of their patients.

4. *Alleged "Unpredictable" Number of PEG-Exendin Conjugate Variants and Alleged "Unpredictability" of Biological Half-Life of Administered Conjugates*

The fact that there may be a large number of possible conjugates useful according to the present invention does not require recitation of each of these variations. The law requires only that the scope of enablement “bear a ‘reasonable correlation’ to the scope of the claims.” MPEP §2164.08, citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As reiterated by MPEP §2164.01, the key in an enablement determination is the word “undue,” not “experimentation.” *See also In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Inventions related to pharmaceuticals, by their nature, always require further testing. Indeed, the Federal Circuit held in *In re Brana*, 34 USPQ2d 1436, 1442-3 (Fed. Cir. 1995), a disclosure complies with the requirements of 35 U.S.C. Section 112, paragraph 1, even though further research and development is required and – “in particular in the context of pharmaceutical inventions” – expected. The Patent Office has not provided any evidence that application of the invention in this case would involve undue experimentation, despite making this contrary assertion.

Applicants submit that enablement of the presently claimed invention does not involve undue experimentation, similar to previous findings of the Federal Circuit. For example, in *In re Wands*, *supra*, Applicants claimed a method for the immunoassay of hepatitis B surface antigen by use of high-affinity IgM antibodies. The Patent Office rejected the claims that were generic to the specified antibodies for alleged want of an enabling disclosure. The Court of Appeals for the Federal Circuit reversed that holding, ruling that one skilled in the art could produce and screen new hybridomas for other monoclonal antibodies falling within the scope of the claims notwithstanding the amount of work this required.

Similarly, given Applicants' disclosure and the state of the art, one skilled in the art would be able to carry out the claimed methods. The claimed methods all relate to "lowering plasma glucagon." Applicants provided multiple working examples as well as other description, which teaches how to measure whether this feature of the invention is accomplished. Certainly the fact that some testing in this regard may be employed by those practicing the invention does not warrant imposition of the present rejection.

Finally, Applicants note the Examiner refers to page 10, lines 15-18, in alleging that the scope of the claims may be broader than the scope of enablement. The discussion of linking the exendin or exendin agonist to one, two or three polyethylene glycol polymers and polyethylene polymers "preferably hav[ing] a molecular weight between 500 and 20,000" on page 10, however, is all with respect to preferred embodiments and certain aspects of the invention, which are described starting on page 8 of the specification. It appears that the Examiner is attempting to impermissibly limit the claims to preferred embodiments of the invention when construing their scope for reasons of comparison with the rest of the specification. *Teleflex Inc. v. Ficosa North America Corp.*, 63 USPQ2d 1374, 1382 (Fed. Cir. 2002); citing *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998), which quotes *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563, 231 USPQ 833, 835 (Fed. Cir. 1986). This attempted construction of the claims cannot legitimize the present rejection.

As a matter of Patent Office practice, a specification disclosure that contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in

compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. In view of the foregoing and applicable law, reconsideration and withdrawal of this rejection is thus warranted and respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

Claims 1-8 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed.

Applicants respectfully submit that under the law of indefiniteness, the Examiner's rejection is inappropriate. 35 U.S.C. Section 112, second paragraph, provides that a specification shall include claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Determining whether a claim is indefinite requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification. . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994); *see also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). So it is with the instant case. As discussed below, one of ordinary skill in the art can readily understand the metes and bounds of the claimed invention. The meaning of the claims is clear and that is all the law requires.

This law is longstanding, well-settled and still in full force and effect. For example, much earlier, the CCPA held in *In re Borkowski*, 442 F.2d 904, 909, 164 USPQ 642, 645-46 (CCPA 1970) (footnotes omitted, emphasis in original):

The first sentence of the second paragraph of §112 is essentially a requirement for *precision and definiteness* of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

The U.S. Court of Appeals for the Federal Circuit recently reiterated this standard for assessing whether a patent claim is sufficiently definite to satisfy 35 U.S.C. §112, second paragraph, in, for example, *Exxon Research and Engineering Co. v. U.S.*, 60 USPQ2d 1272 (Fed. Cir. 2001). There, citing *Miles Labs., Inc. v. Shandon, Inc.*, *supra* at 875, the Federal Circuit held: “If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2.”

Under the law of definiteness, the present claims satisfy 35 U.S.C. §112, second paragraph. Each of the Patent Office’s individual assertions, and the claim(s) affected thereby, is addressed in more detail below.

Claim 1

First, the Examiner contends that claim 1 is indefinite as to line 5 where “an an” was recited because it “is unclear as to whether or not a modified exendin is or is not an exendin agonist; whether or not a modified exendin agonist is or is not exendin agonist; and it is not clear as to what the modifications are compared.” Applicants respectfully disagree that claim 1 is indefinite.

First, Applicants note that claim 1 has been amended to remove the second occurrence of "an" in line 5. This amendment was not made for reasons related to patentability, but was made to correct an obvious typographical redundancy. Hence, the amendment does not alter the scope of claim 1. With or without this typographical correction, the claim is definite and Applicants respectfully request that this rejection be reconsidered and withdrawn.

With respect to the substance of the Examiner's assertion that claim 1 is indefinite, Applicants draw the Examiner's attention to, for example, page 7, lines 13-24, of the specification, which discusses polyethylene glycol (PEG) modification of therapeutic peptides and proteins. As stated therein, "PEG modification may lead to improved circulation time, reduced antigenicity and immunogenicity, improved solubility, resistance to proteolysis, improved bioavailability, reduced toxicity, improved stability, and easier formulation of peptides . . . [. P]roblems with PEGylation in most cases is substantial reduction in bioactivity[,] . . . immunogenicity, instability, toxicity, and reactivity." As set forth, for example, on page 1, lines 17-26, of the specification, modified exendin or modified exendin agonists have "an exendin or exendin agonist peptide linked to one or more polyethylene glycol polymers or other compound[s] useful to decrease renal clearance of the parent peptide." As understandable by those of skill in the art, the modified exendin or exendin agonist is evaluated as compared to the exendin or exendin agonist prior to such modification. Further, on page 9, lines 5-16, of the specification, Applicants teach that certain aspects of the invention relate "to the use of . . . a modified exendin or exendin agonist having an exendin or exendin agonist linked to one or more polyethylene glycol polymers, or other molecular weight enhancing molecules" Example 3 describes clearance of molecules, such as exendins, through the kidneys, followed by

Example 6 describing modifications to exendin 4 that decrease its ability to be filtered by the kidney. Those modifications include increasing the size and/or anionic nature of exendin 4. Page 9, third full paragraph, of the specification describes preferred modified exendins and exendin agonists as having:

a molecular weight that is greater than the molecular weight of the exendin or exendin agonist . . . [,] a negative charge that is greater than the negative charge of the exendin or exendin agonist . . . [,] a kidney clearance that is less than the kidney clearance of the exendin or exendin agonist . . . [, an] immunogenicity/antigenicity that is less than the immunogenicity/antigenicity of the exendin or exendin agonist . . . [,] a solubility that is greater than the solubility of the exendin or exendin agonist . . . [,] a proteolysis rate that is less than the proteolysis rate of the exendin or exendin agonist . . . [,] a toxicity that is less than the toxicity of the exendin or exendin agonist . . . [,] a stability that is greater than the stability of the exendin or exendin agonist . . . [, and] a permeability/biological function that is greater or less than the permeability/biological function of the exendin or exendin agonist .
...

In view of the foregoing, Applicants respectfully submit that claim 1 is indeed definite. Thus, reconsideration and withdrawal of this aspect of the rejection is requested.

Claims 2 and 3

The second asserted basis for this rejection pertains to claims 2 and 3. The Examiner alleges that "it is not clear in the claim recitation per se, what the nexus of the treatment with a glucagon lowering amount of the compound has to the particularly recited disease/condition." For compliance with 35 U.S.C. §112, second paragraph, the claims are read in light of the specification. *Miles, supra*. The Examiner has not proffered any evidence that when claims 2 and 3 are read in the light of the specification, one of ordinary skill in the art would not readily understand the metes and bounds of the claimed invention. Thus, this rejection is not sustainable under the law. There is no requirement under the law that a method of treatment claim that defines the use of a compound to

treat a specific, named condition, provide a “nexus” of treatment. The scope of the claim is clear – use of a composition comprising one or more compounds of claim 1 for the treatment of the conditions of claims 2 and 3 – and Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 6 and 7

The Examiner alleges that claims 6 and 7 are indefinite because the recitation “. . . 1-3 or 4” should read “any one of . . .” The Examiner proffers no evidence or reasoning that one of ordinary skill in the art would not readily understand the metes and bounds of the invention as now claimed. In fact, by suggesting the alternate language set forth in the Office Action, it appears that the Examiner understands the metes and bounds of the claimed invention. Thus, this rejection is also not sustainable under the law as presently asserted.

Claims 7 and 8

Further, the Examiner alleges that claim 7 is indefinite in its recitation of a modified exendin or exendin agonist being linked to one or more polyethylene glycol polymers and makes a similar contention with respect to claim 8. With regard to claim 7, the Examiner inquires “as to (I) how many . . . polyethylene glycol (PEG) polymers are linked to the exendin molecule? (ii) which moiety of the exendin is linked to PEG polymer(s)? (iii) is it α -amine group of the N-terminus or side chain group of the exendin molecule linked to PEG polymer(s)? (iv) are multiple exendin peptides linked to a single PEG polymer? (v) Given the multiple exendin peptides are linked to multiple PEG polymers, whether or not the resultant conjugates are in network state, i.e. macrobiopolymer; if so, if it is water soluble?” With regard to claim 8, the Examiner inquires as to “how many PEG polymers

are conjugated to the exendin molecule? Whether or not is the numbers of PEG-exendin conjugates unlimited?" It is the law that none of the answers to these questions need be provided expressly within the claims themselves, if they need be provided at all.

Page 10, lines 23-31, of the specification teaches:

The polyethylene glycol polymers are preferably linked to an amino, carboxyl, or thio group, and may be linked by N or C termini of side chains of lysine, aspartic acid, glutamic acid, or cysteine, or alternatively, the polyethylene glycol polymers may be linked with diamine and dicarboxylic groups. The exendin or exendin agonist is preferably linked to the polyethylene glycol polymers through an epsilon amino group on a lysine amino acid of the exendin or exendin agonist.

Further, page 49, line 28, to page 50, line 25, describes coupling of polymers to peptides/proteins.

Example 6 exemplifies modification of exendin 4 with a polyethylene glycol (PEG) polymer. Based on the teachings of the specification and general knowledge, one of skill in the art is able to determine the nature and extent of conjugation best suited for the particular use in which the claimed methods will be employed.

As discussed above, claims are read in light of the specification to determine compliance with 35 U.S.C. §112, second paragraph. *Miles, supra*. The Examiner has not proffered any evidence that when claims 7 and 8 are read in the light of the specification, one of ordinary skill in the art would not readily understand the metes and bounds of the claimed invention. Thus, this rejection is not sustainable under the law.

The 35 U.S.C. §102(e) Rejection

Claims 1, 4, and 6 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Fine *et al.* (U.S. Patent No. 6,376,549). This rejection is respectfully traversed.

37 C.F.R. 1.131 provides for swearing back of an alleged reference under 35 U.S.C. §102(e), which show but do not claim the same patentable invention, by showing facts establishing a reduction to practice prior to the effective date of the reference. MPEP §715. Applicants, noting that none of the claims in Fine *et al.* recite exendins, exendin agonists, or modified exendins or exendin agonists, are submitting a Declaration herewith, as contemplated by 37 C.F.R. 1.131. The alleged effective date of Fine *et al.*, appearing on the face of the patent, is the September 17, 1998 filing date of the application leading to the patent.

Applicants do not admit or acknowledge the September 17, 1998 filing date of the application leading to the Fine *et al.* patent to be the effective date of the patent as a 102(e) reference as asserted by the Examiner. As discussed in the attached Declaration, however, Applicants reduced the invention to practice no later than September 2, 1998. The data referenced in the Declaration evidences a method of lowering plasma glucagon in a subject by administering an exendin – exendin-4. At least claims 1, 4 and 5 specifically recite a method directed toward such an embodiment. Thus, the Declaration evidences that the presently claimed invention was reduced to practice no later than September 2, 1998. Specifically, claim 1 was reduced to practice by this date. Claim 1 is the broadest pending claim, being the only independent claim.

As the evidence shows that Applicants reduced the presently claimed invention to practice prior to the effective date of Fine *et al.*, submission of this Declaration is sufficient to overcome this

rejection. Submission of this Declaration shall not be interpreted to be an admission that this rejection is otherwise proper. Withdrawal of the rejection is requested.

The 35 U.S.C. §102(e)/§103(a) Rejection

Claims 1 and 4-8 were rejected under 35 U.S.C. §102(e)/§103(a) as allegedly being obvious over U.S. Patent No. 6,376,549, U.S. Patent No. 6,051,557, PCT Publication No. WO98/30231, and U.S. Patent No. 4,179,397. This rejection is respectfully traversed and deemed overcome by submission of the attached Declaration, which is discussed above and pertains to the first of the four combined documents. Again, submission of this Declaration shall not be interpreted to be an admission that this rejection is otherwise proper.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Young et al.

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By: Lisa M. McGeehan
Lisa M. McGeehan
Reg. No. 41,185

BROBECK, PHLEGER & HARRISON LLP
12390 El Camino Real
San Diego, CA 92130-2081
Telephone: (858) 720-2500
Facsimile: (858) 720-2555

MARKED-UP VERSION OF AMENDED PORTIONS OF SPECIFICATION

Please amend the specification as follows:

Replace the paragraph beginning on page 2, line 21, with the following:

--The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1[7-36]NH₂ [SEQ. ID. NO. 3] (Goke, et al., J. Biol. Chem., 268:19650-55, 1993). GLP-1[7-36]NH₂, also sometimes referred to as proglucagon[78-107] or simply "GLP-1" as used most often herein, has an insulinotropic effect, stimulating insulin secretion from pancreatic beta-cells; Glucagon-like peptide-1 (GLP-1) has also been reported to inhibit glucagon secretion from pancreatic alpha-cells (Ørsov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). GLP-1 has been reported to inhibit gastric emptying (Willms B, et al., J Clin Endocrinol Metab 81 (1) : 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993)). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, is reported to stimulate insulin secretion in humans (Ørskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor said to be responsible at least in part for the insulinotropic effect of GLP-1 has reportedly been cloned from a beta-cell line (Thorens, Proc. Natl. Acad. Sci. USA 89:8641-45, 1992). GLP-1 has been the focus of significant investigation in recent years due to its reported action on the amplification of stimulated insulin production (Byrne MM, Goke B. Lessons from human studies with glucagon-like peptide-1: Potential of the gut hormone for clinical use. In: Fehmann HC, Goke

B. Insulinotropic Gut Hormone Glucagon-Like Peptide 1. Basel, Switzerland: Karger, 1997:219-33).--

Replace the paragraph on page 15, lines 24-26, with the following:

--[Figure 3 depicts] Figures 3A and 3B depict the amino acid sequences for certain exendin agonist compounds useful in the present invention [SEQ. ID. NOS. 10 to 40].--

Replace the paragraph on page 15, lines 27-28, with the following:

--[Figure 4 depicts] Figures 4A1-4J depict the amino acid sequences for certain compounds of the present invention, Compounds 1-174 [SEQ. ID. NOS. 49 to 222].--

Replace the paragraph beginning on page 18, line 22, with the following:

--In support of the investigation of the nonclinical pharmacokinetics and metabolism of exendin-4, a number of immunoassays have been developed. A radioimmunoassay with limited sensitivity (~100 pM) was used in initial pharmacokinetic studies. A two-site immunoradiometric assay (IRMA) [assay] for exendin-4 was subsequently validated with a lower limit of quantitation of 15 pM. The bioavailability of exendin-4, given subcutaneously, was found to be approximately 50-80% using the radioimmunoassay. This was similar to that seen following intraperitoneal administration (48-60%). Peak plasma concentrations (C_{max}) occurred between 30 and 43 minutes (T_{max}). Both C_{max} and area under curve (AUC) values were monotonically related to dose. The apparent terminal half-life for exendin-4 given subcutaneously was approximately 90-110 minutes. This was significantly longer than the 14-41 minutes seen following intravenous dosing. Similar results were obtained using the

IRMA [assay]. Degradation studies with exendin-4 compared to GLP-1 indicate that exendin-4 is relatively resistant to degradation.--

Replace the paragraph on page 55, lines 30-34, with the following:

--Such pharmaceutical compositions are useful in causing glucagon to be lowered in a subject and may be used as well in other disorders where lowered or suppressed glucagon is [beneficially reduced] beneficial.--

Replace the paragraph beginning on page 56, line 16, with the following:

--Generally, in treating or preventing elevated, inappropriate, or undesired post-prandial blood glucagon levels, the compounds of this invention may be administered to patients in need of such treatment in [a] dosage ranges similar to those given above, however, the compounds are administered more frequently, for example, one, two, or three times a day. Particularly preferred are the exendin and exendin agonist formulations and dosages and routes of administration thereof described in commonly owned U.S. Provisional Application 60/116,380, entitled "Novel Exendin Agonist Formulations And Methods of Administration Thereof," filed January 14, 1999 (and the corresponding PCT application claiming priority from it that was filed on January 14, 2000, Serial No. PCT/US00/00902 [[not yet assigned]]), and U.S. Provisional Application 60/175,365 [60/[not yet assigned]], entitled "Use of Exendins and Agonists Thereof for Modulation of Triglyceride Levels and Treatment of Dyslipidemia," filed January 20, 2000, [14, 1999], from which this application claims priority and the disclosures of which have been incorporated by reference in their entirety as if fully set forth herein.--

Replace the paragraph beginning on page 58, line 14, with the following:

--The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical reversed-phase high performance liquid chromatography (RP-HPLC) (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.2 minutes.--

Replace the paragraph bridging pages 64 and 65 with the following:

--Many of the methods for covalent attachment of PEG take advantage of the epsilon-amino group on lysine. Exendin 4 has two lysines that can be modified by attachment of PEG. An alanine scan of AC3177 (Leu¹⁴, Phe²⁵1-28 exendin-4), a shortened analog of exendin 4, revealed positions that are sensitive to substitution by alanine. The two lysines at positions 12 and 27 were moderately affected by this substitution suggesting that loss of the lysine specific R group side chain (methylene chain plus epsilon-amino group) is tolerated. With regard to the full-length peptide, exendin 4, the two lysine positions are appropriate for PEG attachment (see compounds 201 and 202). In addition, depending on the chemistry used to conjugate the PEG, the epsilon-amino groups at these positions may be masked thereby increasing the anionic nature of the peptide.

(201) HGEGTFTSDLSK(PEG)QMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO. 223]

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- (202) HGETFTSDL SKQMEEEAVRLFIEWLK(PEG)NGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
224].--

Replace the paragraph on page 65, lines 5-20, with the following:

--Based on the results of the alanine scan, other likely positions that may be modified by insertion of a Lys-PEG or equivalent, for example, are:

- (203) HK(PEG)EGTFTSDL SKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
225]

- (204) HEGK(PEG)FTSDL SKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
226]

- (205) HGETFTK(PEG)DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
227]

- (206) HGETFTSDK(PEG)SKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
228]

- (207) HGETFTSDLK(PEG)KQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
229]

- (208) HGETFTSDL SKKK(PEG)MEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
230]

- (209)* HGETFTSDL SKQMEK(PEG)EAVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
231]

- (210)* HGETFTSDL SKQMEEK(PEG)AVRLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
232]

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- (211) HGETFTSDLSKQMEEEAK(PEG)RLFIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
233]
- (212) HGETFTSDLSKQMEEEAVRK(PEG)FIEWLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
234]
- (213)* HGETFTSDLSKQMEEEAVRLFIK(PEG)WLKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
235]
- (214) HGETFTSDLSKQMEEEAVRLFIEK(PEG)LKNGGPSSGAPPPS-NH₂ [SEQ. ID. NO.
236]
- (215) HGETFTSDLSKQMEEEAVRLFIEWLKK(PEG)GGPSSGAPPPS-NH₂ [SEQ. ID. NO.
237].--

Replace the paragraph beginning on page 65, line 21, with the following:

--The three positions* above normally containing a glutamic acid that were indicated for modification with K(PEG) can also be modified by conjugation to the glutamic acid side chain carboxyl group, E(PEG).--

Replace the paragraph on page 65, lines 25-28, with the following:

--Another analog in which the Lys-PEG can be added is at the supposed GlyGly turn:

- (216) HGETFTSDLSKQMEEEAVRLFIEWLKNK(PEG)GPSSGAPPPS-NH₂ [SEQ. ID. NO.
238]
- (217) HGETFTSDLSKQMEEEAVRLFIEWLKNGK(PEG)PSSGAPPPS-NH₂ [SEQ. ID. NO.
239].--

MARKED-UP VERSION OF AMENDED CLAIMS

1. (Once Amended) A method of lowering plasma glucagon in a subject, comprising administering to said subject a therapeutically effective glucagon lowering amount of a compound selected from [the group consisting of] an exendin, an [an] exendin agonist, a modified exendin and a modified exendin agonist.